# Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling

Fröhlich, G ; Steffel, J ; Hürlimann, D ; Enseleit, F ; Lüscher, T F ; Ruschitzka, F ; Abraham, W T ; Holzmeister, J

Abstract: AIMS: Chronic right ventricular (RV) pacing may impose ventricular dyssynchrony leading to LV remodelling and is associated with increased morbidity and mortality. Upgrading patients with chronic RV pacing to cardiac resynchronization therapy (CRT) may be considered to restore synchronicity and prevent these deleterious effects. METHODS AND RESULTS: A total of 172 patients from two tertiary centres were analysed over a mean follow-up of 21.7 and 23.5 months after primary CRT implantation (n = 102) and CRT upgrade (n = 70), respectively. In the latter group, mean duration of RV pacing before CRT upgrade was 80.3 months, and ventricular stimulation was >95%. A significant improvement in left ventricular (LV) ejection fraction (10 and 11% absolute increase in primary CRT vs. upgrades, respectively), LV end-diastolic diameter index (-0.15 cm/m(2) vs. -0.2 cm/m(2)), and LV end-systolic diameter (-6.0 vs. -7.0 mm) was observed in both groups, which did not differ between primary CRT recipients and CRT upgrades. Response to CRT upgrade was independent of the underlying rhythm, QRS duration, duration of prior RV pacing, or LV function and size at baseline. Of note, even seven of nine patients with RV pacing >12 years responded favourably to CRT. CONCLUSION: The current study demonstrates that CRT reverses LV remodelling in heart failure patients with chronic RV pacing in a similar way as in primary CRT recipients, even after very long periods of RV pacing. Our data, therefore, may have important implications for the treatment of pacemaker-dependent patients with heart failure, and support the use of CRT in this setting.

DOI: https://doi.org/10.1093/eurheartj/ehq065

European Heart Journal (2010) **31**, 1477–1485
doi:10.1093/eurheartj/ehq065



# Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling

**Georg Fröhlich[1†], Jan Steffel[1†], David Hürlimann[1], Frank Enseleit[1], Thomas F. Lüscher[1], Frank Ruschitzka[1], William T. Abraham[2], and Johannes Holzmeister[1,2*]**

[1]Cardiovascular Center, Cardiology, University Hospital Zurich, Raemistrasse 100, Zurich CH-8091, Switzerland; and [2]Division of Cardiovascular Medicine, Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH, USA

*Received 29 October 2009; revised 21 December 2009; accepted 5 January 2010; online publish-ahead-of-print 16 March 2010*

**This paper was guest edited by Jeroen J. Bax, Leiden University Medical Center, Leiden, The Netherlands**

**Aims** Chronic right ventricular (RV) pacing may impose ventricular dyssynchrony leading to LV remodelling and is associated with increased morbidity and mortality. Upgrading patients with chronic RV pacing to cardiac resynchronization therapy (CRT) may be considered to restore synchronicity and prevent these deleterious effects.

**Methods and results** A total of 172 patients from two tertiary centres were analysed over a mean follow-up of 21.7 and 23.5 months after primary CRT implantation ($n = 102$) and CRT upgrade ($n = 70$), respectively. In the latter group, mean duration of RV pacing before CRT upgrade was 80.3 months, and ventricular stimulation was >95%. A significant improvement in left ventricular (LV) ejection fraction (10 and 11% absolute increase in primary CRT vs. upgrades, respectively), LV end-diastolic diameter index ($-0.15$ cm/m$^2$ vs. $-0.2$ cm/m$^2$), and LV end-systolic diameter ($-6.0$ vs. $-7.0$ mm) was observed in both groups, which did not differ between primary CRT recipients and CRT upgrades. Response to CRT upgrade was independent of the underlying rhythm, QRS duration, duration of prior RV pacing, or LV function and size at baseline. Of note, even seven of nine patients with RV pacing >12 years responded favourably to CRT.

**Conclusion** The current study demonstrates that CRT reverses LV remodelling in heart failure patients with chronic RV pacing in a similar way as in primary CRT recipients, even after very long periods of RV pacing. Our data, therefore, may have important implications for the treatment of pacemaker-dependent patients with heart failure, and support the use of CRT in this setting.

**Keywords** Cardiac resynchronization therapy • Right ventricular pacing • CRT upgrade

## Introduction

Biventricular pacing (cardiac resynchronization therapy, CRT) has been shown to reduce morbidity and mortality in heart failure patients with a left ventricular (LV) ejection fraction (LVEF) <35% and a wide QRS complex (>120 ms).[1–3] In these patients, LV function is impaired as a result of asynchronous contractions of the different segments within the left ventricle as well as between the right and left ventricle. Concomitant pacing with a coronary sinus lead implanted in a lateral or posterolateral vein resynchronizes the contraction, resulting in reverse LV remodelling with a decrease in LV size and an increase in LVEF.[4–6] The extent of LV reverse remodelling is of crucial importance, as it directly relates to the long-term prognosis after CRT.[7,8]

Right ventricular (RV) apical pacing by a permanent pacemaker is the standard treatment for patients with severe bradyarrhythmias. However, RV pacing (like left bundle branch block) leads to a delayed activation of lateral LV segments resulting in intra- and

† The first two authors contributed equally to the study.

* Corresponding author. Tel: +41 44 255 24 38, Fax: +41 44 255 44 01, Email: johannes.holzmeister@usz.ch

**Table 1 Baseline parameters**

| Characteristic | Primary CRT | CRT upgrade | *P*-value |
|---|---|---|---|
| Patients (*n*, %) | 102/172 (59.3) | 70/172 (40.7) | |
| Demographics | | | |
| Age at implantation (years) | 61.0 (54–67)[a] | 66.5 (57.0–75.0)[a] | 0.005 |
| Male (*n*, %) | 82 (80.4) | 51 (72.9) | 0.25 |
| Underlying heart disease (*n*, %) | | | 0.74 |
| Ischaemic cardiomyopathy | 41 (40.2) | 36 (51.4) | |
| Non-ischaemic cardiomyopathy | 61 (59.8) | 34 (48.6) | |
| Duration of right ventricular pacing (months) | | 60.0 (43.8–96.0) | |
| Average ventricular stimulation (% of time) | | 99 (90–100) | |
| NYHA class (*n*, %) | | | 0.2 |
| I | 0 | 0 | |
| II | 20 (20) | 20 (29) | |
| III | 76 (75) | 48 (69) | |
| IV | 5 (5) | 2 (3) | |
| Echocardiographic baseline parameters | | | |
| LV ejection fraction (%) | 20.0 (16.8–29.0) | 24.0 (17.8–30.0) | 0.12 |
| End-diastolic volume (mL)[b] | 244 (175–305) | 219 (141–259) | 0.07 |
| End-diastolic volume index (mL/m$^2$)[b] | 120 (92–144) | 104 (82–134) | 0.15 |
| End-systolic volume (mL)[b] | 183 (134–252) | 164 (95–217) | 0.12 |
| End-systolic volume index (mL/m$^2$)[b] | 92.2 (66.9–115) | 83.1 (53.8–111) | 0.18 |
| LV end-diastolic diameter (mm) | 70.0 (60.0–78.8)[a] | 64.0 (57.5–71.0)[a] | 0.008 |
| LV end-diastolic diameter index (cm/m$^2$) | 3.5 (3.0–3.9) | 3.2 (3.0–3.6) | 0.03 |
| LV end-systolic diameter (mm) | 60.0 (52.0–69.0)[a] | 54.5 (46.0–62.0)[a] | 0.002 |
| Left ventricular muscle mass index (g/m$^2$)[b] | 165 (150–194) | 149 (109–201) | 0.48 |
| Pulmonary artery pressure (mmHg) | 34.5 (25.0–40.8) | 31.0 (23.3–38.8) | 0.46 |
| Left atrium index (cm/m$^2$) | 2.4 (2.2–2.8) | 2.6 (2.2–3.1) | 0.35 |
| Degree of mitral regurgitation (*n*, %) | | | 0.31 |
| Mild | 73 (74) | 41 (66) | |
| Moderate | 18 (18) | 14 (23) | |
| Severe | 8 (8) | 7 (11) | |
| Rhythm at time of implantation | | | |
| Sinus rhythm/VAT pacing | 70 (68.6) | 33 (47.1) | 0.005 |
| Atrial fibrillation (*n*, %) | 32 (31.4) | 37 (52.9) | 0.005 |
| QRS width (ms) | 154 (133–178)[a] | 184 (163–205)[a] | <0.001 |
| Pharmacologic therapy at time of implantation (*n*, %) | | | |
| Beta-blockers | 91 (89.2) | 63 (90) | 0.87 |
| ACE-inhibitors | 77 (75.5) | 45 (64.3) | 0.11 |
| AT receptor blockers | 20 (19.6) | 22 (31.4) | 0.08 |
| Diuretics | 84 (82.4) | 49 (70.0) | 0.09 |
| Aldosterone antagonists | 53 (52) | 33 (47.1) | 0.54 |
| Aspirin | 58 (56.9) | 36 (51.4) | 0.49 |
| Oral anticoagulation | 43 (42.2) | 41 (58.6) | 0.03 |

Number of patients (%) and median (25–75 percentile) are shown for categorical and continuous data, respectively. AF, atrial fibrillation; ACE, angiotensin converting enzyme; AT, angiotensin; CRT, cardiac resynchronization therapy; LV, left ventricular; NYHA, New York Heart Association.

[a]Not normally distributed.

[b]$n = 69$.

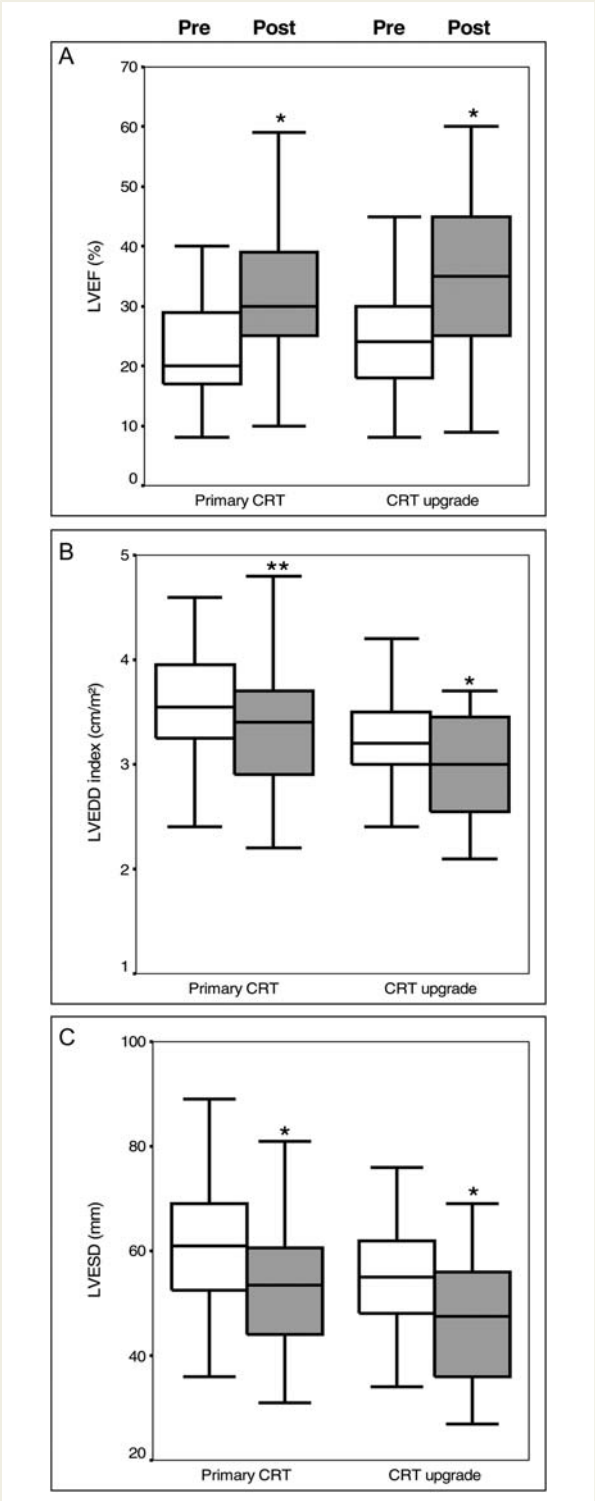


**Figure 1** Response to CRT in primary and CRT upgrade recipients. A significant improvement in left ventricular ejection fraction (LVEF, *A*), left ventricular end-diastolic diameter (LVEDD, *B*), and left ventricular end-systolic diameter (LVESD, *C*) was observed both after primary CRT implantation and after CRT upgrades. *$P < 0.0001$ vs. baseline in primary CRT group or in CRT upgrade group, **$P = 0.001$ vs. baseline in primary CRT group. 'Pre' and 'Post' denote values before and after CRT implantation, respectively.

interventricular dyssynchrony. As such, chronic RV pacing has been shown to induce LV remodelling, impair LV function, and increase the severity of mitral regurgitation.[9–12] As a result, long-term RV pacing may be deleterious and has been associated with increased morbidity and mortality.[13,14] 'Upgrading' these patients to CRT therefore intuitively appears reasonable to correct dyssynchrony. Previous studies examining the effect of biventricular pacing on LV remodelling, however, were limited due to small patient numbers and relatively short follow-up periods.[15–18] The current study was hence designed to assess the long-term effect of CRT on reverse LV remodelling in a large cohort of heart failure patients upgraded to CRT after chronic RV pacing, and compare it with that observed after primary CRT implantation.

# Methods

## Study population

We retrospectively reviewed 69 consecutive patients at the University Hospital of Zurich and 103 consecutive patients at Ohio State University, who underwent either primary CRT implantation or CRT upgrade between 2001 and 2008, and for whom echocardiographic follow-up data at least 6 months after CRT implantation were available. At the time of implantation, patients were managed by a heart failure specialist and were on optimal medical heart failure therapy including a beta-blocker as well as an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker (unless contraindicated or not tolerated, *Table 1*).

Cardiac resynchronization therapy upgrade recipients had a pacemaker implanted for a standard bradycardia indication or after atrioventricular (AV) node ablation for refractory atrial fibrillation. Mean duration of RV pacing before the upgrade procedure was 80.3 months; average percent of ventricular stimulation had to be in excess of 50% for at least 6 months for a patient to be included (*Table 1*). Patients were selected for CRT implantation based on current standard criteria and guidelines.[19]

## Echocardiography

Only subjects in whom echocardiographic follow-up data were available were included in the study. Patients underwent baseline echocardiography before the implantation procedure and at least 6 months thereafter. Standard parameters including LVEF (as assessed by biplane Simpson's rule in apical four- and two-chamber view), LV end-diastolic diameter and LV end-diastolic diameter index, LV end-systolic diameter, left atrial index, the degree of mitral regurgitation (as recorded on a semi-quantitative scale), and pulmonary artery pressure (as estimated from tricuspid regurgitation using CW-Doppler) were recorded whenever available. Patients demonstrating an absolute increase in LVEF of at least 10% at follow-up were considered responders to CRT.

## Biventricular pacemaker implantation

Biventricular pacemaker implantation was performed following standard protocols, using either a left or right cephalic or subclavian venous access. Retrograde venous angiography was performed to facilitate optimal positioning of the LV lead into the coronary sinus. The LV lead was preferably implanted in the lateral or postero-lateral mid-ventricular region of the left ventricle whenever possible.

**Table 2 Follow-up of primary cardiac resynchronization therapy recipients and upgrades**

| Characteristic | Primary CRT | CRT upgrade | *P*-value |
|---|---|---|---|
| Time of last FUP (months after CRT implantation; mean ± SD) | 21.7 ± 14.2 | 23.5 ± 15.2 | 0.43 |
| | Δ At last FUP | Δ At last FUP | |
| Echocardiographic parameters | | | |
| LV ejection fraction (%) | 10.0 (3.8–15.0) | 10.0 (5.0–20.0) | 0.61 |
| End-diastolic volume (mL)[a] | −34.0 (−72.5 to 13.0) | −20.0 (−73 to −1.0) | 0.67 |
| End-diastolic volume index (mL/m$^2$)[a] | −16.0 (−33.8 to 7.0) | −11.0 (−35.5 to 0.0) | 0.55 |
| End-systolic volume (mL)[a] | −35.3 (−75.1 to −6.9) | −26.0 (−78.6 to −6.1) | 0.68 |
| End-systolic volume index (mL/m$^2$)[a] | −17.4 (−35.5 to −3.3) | −14.9 (−38.3 to −2.5) | 0.61 |
| LV end-diastolic diameter index (cm/m$^2$) | −0.15 (−0.4 to 0.08) | −0.2 (−0.6 to 0) | 0.66 |
| LV end-diastolic diameter (mm) | −2.0 (−12.5 to 1.0) | −5.0 (−13.0 to 0) | 0.56 |
| LV end-systolic diameter (mm) | −6.0 (−13.8 to −0.25) | −7.0 (−16.0 to −0.75) | 0.89 |
| Left ventricular muscle mass index (g/m$^2$)[a] | −11 (−40 to −6) | −14.0 (−56.5 to 9.5) | 0.67 |
| Pulmonary artery pressure (mmHg) | 0 (−15.3 to 8.0) | −5.0 (−11.0 to 1.0) | 0.42 |
| Left atrium index (cm/m$^2$) | −0.1 (−0.3 to 0) | −0.1 (−0.2 to 0) | 0.52 |
| Change in mitral regurgitation (*n*, %) | | | 0.22 |
| Improved by two levels | 3 (3) | 1 (2) | |
| Improved by one level | 15 (16) | 16 (28) | |
| no change | 71 (74) | 38 (66) | |
| worsened | 7 (7) | 3 (5) | |
| Change in NYHA functional class (*n*, %) | | | 0.51 |
| Improved by two or more classes | 4 (4) | 2 (3) | |
| Improved by one class | 48 (47) | 35 (50) | |
| No change | 43 (42) | 30 (43) | |
| Worsened | 3 (3) | 2 (3) | |
| QRS duration (ms) | −11.0 (−26.5 to 14.5)[b] | −28.0 (−44.0 to −6.0)[b] | 0.001 |
| Pharmacological therapy at follow-up (*n*, %, change to baseline, *n*) | | | |
| Beta-blockers | 92 (90) | 63 (90) | 0.65 |
| ACE-inhibitors | 69 (68) | 40 (57) | 0.11 |
| AT receptor blockers | 26 (26) | 25 (36) | 0.18 |
| Diuretics | 81 (79) | 48 (69) | 0.44 |
| Aldosterone antagonists | 59 (58) | 29 (41) | 0.03 |
| Aspirin | 54 (53) | 38 (54) | 0.97 |
| Oral anticoagulation | 48 (47) | 47 (67) | 0.01 |

Number of patients (%) and median (25–75 percentile) are shown for categorical and continuous data, respectively, unless indicated otherwise. CRT, cardiac resynchronization therapy; FUP, follow-up; NYHA, New York Heart Association; LV, left ventricular.
[a]$n = 69$.
[b]Not normally distributed.

## Statistics

Comparison of categorical variables was performed by $\chi^2$ and Fisher's exact test (in case of low sample sizes). The influence of the aetiology of heart failure, underlying heart rhythm, QRS width, and duration of preceding RV pacing on CRT response rate was assessed using Pearson's $\chi^2$ test. Continuous variables within the same group (i.e. comparison of variables before and after CRT implantation) were analysed by two-sided paired Student's *t*-test (for normally distributed variables) or Wilcoxon signed-rank test (for non-normally distributed variables). Continuous variables between groups (i.e. comparison between primary CRT implantation and CRT upgrade) were analysed by unpaired two-sided Student's *t*-test (for normally distributed variables) or Mann–Whitney *U* test (for non-normally distributed variables). Confidence intervals were calculated using the *t*-test. A *P*-value $< 0.05$ was considered significant. Statistical analysis was performed using SPSS Ver 17.0 (SPSS, Inc., Chicago, IL, USA).

# Results

## Baseline parameters

Baseline characteristics are summarized in *Table 1*. Patients with primary CRT implantation were younger than those receiving CRT upgrades. The distribution of the underlying cardiomyopathy

**Table 3 Follow-up parameters in cardiac resynchronization therapy responders**

| Characteristic | Primary CRT | CRT upgrade | *P*-value |
|---|---|---|---|
| Responders, *n* (%) | 57/102 (55.9) | 39/70 (55.7) | 0.98 |
| Aetiology of heart failure | | | 0.32 |
| Ischaemic heart failure | 20/57 (35.1) | 15/39 (38.5) | |
| Non-ischaemic heart failure | 37/57 (64.9) | 24/39 (61.5) | |
| Echocardiographic parameters | | | |
| Δ LV ejection fraction (%) | 15.0 (11.5–20.5) | 17.0 (13.0–22.0) | 0.58 |
| Δ LV end-diastolic diameter index (cm/m$^2$) | −0.3 (−0.5 to 0) | −0.3 (−0.7 to −0.1) | 0.90 |
| Δ LV end-diastolic diameter (mm) | −7.0 (−14.0 to −1.0) | −11.0 (−14.5 to −2.5) | 0.84 |
| Δ LV systolic diameter (mm) | −10 (−19.8 to −3.5) | −12.0 (−16.0 to −3.0) | 0.82 |
| Δ Left atrium index (cm/m$^2$) | −0.1 (−0.38 to 0) | 0 (−0.15 to 0.25) | 0.49 |
| Change in mitral regurgitation | | | 0.02 |
| Improved by two levels | 0 | 1 (3) | |
| Improved by one level | 7 (13) | 9 (28) | |
| No change | 45 (79) | 22 (69) | |
| Worsened | 2 (4) | 0 | |
| Δ Pulmonary artery pressure (mmHg) | −1.0 (−16.0 to 6.75) | −5.5 (−12.8 to 1.0) | 0.31 |
| Change in NYHA functional class (*n*, %) | | | 0.18 |
| Improved by two or more classes | 3 (6) | 2 (5) | |
| Improved by one class | 34 (62) | 24 (63) | |
| No change | 18 (33) | 28 (29) | |
| Worsened | 0 | 1 (3) | |
| Δ QRS (ms) | −6.0 (−22 to 12)[a] | −24 (−43 to −6.0)[a] | 0.02 |

Number of patients (%) and median (25–75 percentile) are shown for categorical and continuous data, respectively. CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; LV, left ventricular.
[a]Not normally distributed.

was similar among the two groups. Patients receiving primary CRT implantation had higher LV end-diastolic and end-systolic diameters, whereas end-diastolic and end-systolic volumes were similar. Atrial fibrillation (as well as concomitant oral anticoagulation) was more common in patients with CRT upgrade procedures. Pharmacological heart failure therapy was optimized in both groups.

## Echocardiographic and clinical follow-up

Left ventricular ejection fraction, LV end-diastolic diameter index, and LV end-systolic diameter at baseline and at the time of last follow-up are shown in *Figure 1*. Left ventricular ejection fraction increased from 20.0 to 30.0% and from 24.0 to 35.0% in primary CRT and in CRT upgrade recipients, respectively. Likewise, LV end-diastolic diameter index and LV end-systolic diameter improved in primary CRT recipients (3.5–3.2 cm/m$^2$ and 6.0–5.2 cm, respectively) and in CRT upgrade patients (3.2–3.0 cm/m$^2$ and 5.5–4.5 cm, respectively).

Comparison of follow-up data after primary CRT implantation and CRT upgrade are presented in *Table 2*. Mean follow-up was 21.7 and 23.5 months after primary CRT implantation and CRT upgrade, respectively. Both groups displayed a similar improvement in LVEF, LV end-systolic and end-diastolic diameters, pulmonary artery pressure, left atrial size, and degree of mitral regurgitation. Improvement in NYHA functional class was equally comparable. As expected, pre-CRT QRS duration was significantly longer in patients with chronic RV pacing (*Table 1*) and was reduced more dramatically after CRT implantation (*Tables 2* and *3*).

Comparison of primary CRT responders with CRT upgrade responders are presented in *Table 3*. No difference in the rate of responders, the aetiology of the underlying heart failure, or the improvement in echocardiographic parameters was observed between the two groups, except for a slightly more pronounced improvement in the degree of mitral regurgitation in the CRT upgrade group.

## Responder characteristics

Baseline characteristics of responder patients receiving CRT upgrades are summarized in *Table 4*, separated according to responder status. Cardiac resynchronization therapy upgrade patients with underlying ischaemic heart failure were less likely to respond to CRT when compared with those with a non-ischaemic aetiology of reduced LV function. No other baseline parameters, including underlying rhythm, QRS duration, duration of prior RV pacing, or echocardiographic parameters were distinctly predictive of response to CRT.

Baseline characteristics of responder patients receiving primary CRT are summarized in *Table 5*. No baseline parameter, including

**Table 4 Baseline parameters of cardiac resynchronization therapy upgrade patients**

| Characteristic | Responder | Non-responder | *P*-value |
|---|---|---|---|
| Underlying cardiomyopathy | | | |
| Ischaemic | 15/36 (41.7) | 21/36 (58.3) | 0.01 |
| Non-ischaemic | 24/34 (70.6) | 10/34 (29.4) | |
| Underlying rhythm | | | 0.30 |
| VAT pacing | 20/33 (60.6) | 13/33 (39.4) | |
| Atrial fibrillation | 19/37 (51.4) | 18/37 (48.6) | |
| QRS duration at implantation | | | 0.57 |
| <120 ms | 1/1 (100) | 0/1 (0) | |
| 121–150 | 5/5 (100) | 0/5 (0) | |
| 151–180 ms | 8/21 (38.1) | 13/21 (61.9) | |
| >180 ms | 23/38 (60.5) | 15/38 (39.5) | |
| QRS (ms) | 186 (163–209) | 181 (174–201) | 0.90 |
| Duration of right ventricular pacing | | | 0.74 |
| <24 months | 4/6 (66.7) | 2/6 (33.3) | |
| 25–60 months | 17/31 (54.8) | 14/31 (45.2) | |
| 61–96 months | 9/18 (50) | 9/18 (50) | |
| 96–144 months | 2/6 (33.3) | 4/6 (66.7) | |
| > 144 months | 7/9 (77.8) | 2/9 (22.2) | |
| Duration of RV pacing | 60.0 (36.0–96.0) | 60.0 (48.0–85.0) | 0.53 |
| Echocardiographic parameters | | | |
| LVEF at implant | 25.0 (20.0–30.0) | 22.0 (16.0–30.0) | 0.15 |
| <20% | 8/18 (44.4) | 10/18 (55.6) | 0.39 |
| 20–30% | 24/40 (60) | 16/40 (40) | |
| >30% | 7/12 (58.3) | 5/12 (41.7) | |
| LVEDD index (cm/m$^2$) | 3.0 (2.8–3.7) | 3.3 (3.0–3.5) | 0.82 |
| LVESD (mm) | 50.0 (45.0–60.0) | 56.0 (52.5–64.0) | 0.07 |
| Left atrium index (cm/m$^2$) | 2.6 (2.1–3.1)[a] | 2.7 (2.3–3.1)[a] | 0.90 |
| Pulmonary artery pressure (mmHg) | 31.0 (23.3–37.5) | 30.5 (23.5–40.0) | 0.67 |

Number of patients (%) and median (25–75 percentile) are shown for categorical and continuous data, respectively. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RV, right ventricular.
[a]Not normally distributed.

the aetiology of heart failure, underlying rhythm, QRS duration, or echocardiographic parameters were predictive of CRT response in this group of patients.

# Discussion

Chronic RV pacing has been shown to induce pathologic LV remodelling, including LV dilation and a reduction in LVEF, due to 'extrinsically' imposed dyssynchrony.[9,11] 'Upgrading' these patients to CRT to restore synchronicity may therefore be a reasonable therapeutic option. Our data demonstrate that CRT upgrade after chronic RV pacing results in a similar improvement in LVEF and reduction in LV dimensions as observed in heart failure patients after primary CRT implantation. Interestingly, our data further indicate that CRT significantly reverses LV remodelling even after long-term (up to 10 years) RV pacing. These results are of particular interest as long-term survival after CRT has been shown to be predicted by the degree of LV reverse remodelling in patients undergoing primary CRT implantation.[7,8]

A few small-scale single centre studies have previously investigated the short-term changes in LV remodelling after upgrading chronically RV-paced heart failure patients to CRT. One study demonstrated an acute improvement in LVEF and LV size in 15 patients upgraded to CRT.[16] Similar results were observed in a group of 20 heart failure patients with atrial fibrillation and AV-node ablation 6 months after being upgraded to CRT.[15] Although no direct comparison with primary CRT recipients was performed in these early investigations, two more recent short-term studies compared the effect of CRT on LV remodelling in patients with CRT upgrade and primary CRT implantation. In the first study, LVEF improved at least 5% in both groups after 3 months of follow-up.[18] In the second very recent study, an increase in LVEF of 13.7 and 8.7% was observed after 1-year follow-up with primary vs. upgrade CRT implantation, respectively.[20] All of the above-mentioned studies, however, are limited

**Table 5 Baseline parameters of primary cardiac resynchronization therapy recipients**

| Characteristic | Responder | Non-responder | *P*-value |
|---|---|---|---|
| Underlying cardiomyopathy | | | 0.24 |
| Ischaemic | 20/41 (48.8) | 21/41 (51.2) | |
| Non-ischaemic | 37/61 (60.7) | 24/61 (39.3) | |
| Underlying rhythm | | | 0.38 |
| Sinus rhythm | 41/70 (58.6) | 29/70 (41.4) | |
| Atrial fibrillation | 16/32 (50) | 16/32 (50) | |
| QRS duration at implantation | | | 0.34 |
| <120 ms | 9/13 (69.2) | 4/13 (30.8) | |
| 121–150 | 19/31 (61.3) | 12/31 (38.7) | |
| 151–180 ms | 14/31 (45.2) | 17/31 (54.8) | |
| >180 ms | 10/17 (58.8) | 7/17 (41.2) | |
| QRS (ms) | 148 (129–178) | 166 (135–178) | 0.24 |
| Echocardiographic parameters | | | |
| LVEF at implantation | 20.0 (15.0–27.0) | 23.0 (17.0–30.0) | 0.63 |
| <20% | 20/36 (55.6) | 16/36 (44.4) | 0.99 |
| 20–30% | 31/55 (56.4) | 24/55 (43.6) | |
| >30% | 6/11 (54.5) | 5/11 (45.5) | |
| LVEDD index (cm/m$^2$) | 3.4 (3.0–3.9) | 3.6 (3.2–3.9) | 0.80 |
| LVESD (mm) | 60.0 (50.5–67.0) | 61.0 (52.0–75.3) | 0.15 |
| Left atrium index (cm/m$^2$) | 2.25 (2.0–2.4)[a] | 2.6 (2.2–2.8)[a] | 0.01 |
| Pulmonary artery pressure (mmHg) | 31.0 (25.0–41.0) | 36.0 (28.0–40.5) | 0.36 |

Number of patients (%) and median (25–75 percentile) are shown for categorical and continuous data, respectively. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.
[a]Not normally distributed.

by a rather low patient number, short follow-up period, and lack of comprehensive analysis of LV remodelling. In contrast, our data demonstrate for the first time the beneficial effect of CRT on several parameters of LV remodelling in a large cohort of patients receiving CRT upgrade after chronic RV pacing and show that a similar response may be expected as after primary CRT implantation. Importantly, all patients were managed by heart failure specialists, and were maintained on optimal medical therapy both at the time of implantation (*Table 1*) as well as during follow-up (*Table 2*).

There is currently no gold standard for the definition of response to CRT.[21] Previous studies have frequently used combined clinical and/or echocardiographic criteria to assess response to CRT upgrade after chronic RV pacing.[20,22] The use of clinical endpoints, however, may in itself be problematic, especially in a non-randomized, non-blinded study design. Furthermore, LV remodelling, but not clinical improvement, is related to and may predict long-term survival after CRT.[7,8] Therefore, an absolute increase in LVEF of ≥10% was used to define response to CRT in our study. Using this cut-off, which in our opinion clearly resembles a significant therapeutic effect, the rate of responders to CRT was similar between the two groups. Furthermore, we also observed no difference in the proportion of responders between the two groups when using a different cut-off value (e.g. increase in LVEF > 5%) for response (data not shown).

Of note, some differences in baseline characteristics were observed between patients receiving primary CRT implantation when compared with those with CRT upgrades (e.g. age, LV end-diastolic and end-systolic diameter, rhythm at time of implantation), which may have introduced a certain degree of bias in the intergroup analyses in this non-randomized study. However, a comparable absolute response to CRT in the intra-group analyses was observed with a similar improvement in LV reverse remodelling. Indeed, the overall response to CRT within each group was largely independent of the underlying rhythm, QRS duration, LVEF, LV size, and duration of prior RV pacing, indicating a similar response potential in all subgroups of patients. In this retrospective analysis, LV volumes were only available in 69 patients. There was no difference in baseline LV volumes or the improvement in LV volumes between primary CRT recipients and CRT upgrades. Together with the similar improvement in LVEF and LV diameters between the two groups, these data strongly suggest that CRT indeed results in a comparable degree of LV reverse remodelling in both primary CRT and CRT upgrade recipients.

Patients with CRT upgrades were older than those with primary CRT implantation, and more frequently presented with atrial fibrillation, which is in line with previous data,[20] and may be explained by a subgroup of patients in the CRT upgrade group, who initially underwent pacemaker implantation and AV nodal ablation due to

refractory atrial fibrillation. The response to CRT, however, was independent of the underlying rhythm both in patients receiving CRT upgrades and after primary CRT implantation. As expected, baseline QRS duration was longer in patients with chronic RV pacing compared with primary CRT patients. As a consequence, the reduction of QRS duration was more dramatic in the first when compared with the latter group. However, response to CRT in both groups was largely independent of baseline QRS duration, and was observed in patients both with little and with pronounced conduction delay.

Patients with ischaemic cardiomyopathy receiving CRT upgrades were less likely to respond to CRT than those with a non-ischaemic aetiology as the cause of ventricular dysfunction. On the other hand, patients receiving primary CRT implantation in our cohort had a similar response rate independent of the underlying type of cardiomyopathy, which is somewhat in contrast to large-scale primary CRT studies such as CARE-HF, in which the presence of ischaemic heart disease was predictive of a worse outcome.[23] This difference may, however, be related to the echocardiographic criteria used to define response to CRT in our study (when compared with the combined clinical endpoint in CARE-HF). Furthermore, several criteria known to affect response such as myocardial viability or presence of myocardial scars[24,25] were routinely taken into consideration before primary CRT implantation in patients with ischaemic cardiomyopathy, and may have resulted in a selection of patients who are more likely to respond to CRT. In this context, a priori identification of patients most likely to respond to CRT upgrade would be of interest. It is conceivable that the response to CRT upgrade, similar to primary CRT implantation, is largely influenced by the extent of scar tissue and viable myocardium, especially in the LV pacing lead region. However, the current study was primarily designed to investigate whether CRT upgrade patients show evidence of LV remodelling, and not to comprehensively assess predictors of response; hence, further studies are required in this regard. For the time being and in the absence of conclusive data, it is current practice of the authors to apply the same eligibility and selection criteria for patients receiving CRT upgrades as for primary CRT recipients.

Chronic RV pacing may induce LV remodelling and consequently lead to worsening LV function.[9–12] On an individual basis, however, it is difficult if not impossible to discern whether a decrease in LV function occurs as a result of RV pacing or as a consequence of the natural course of the underlying cardiomyopathy. The current study was hence not designed to address the differential contribution of these two effects to the precedent deterioration of LV function but to examine the effect of CRT upgrade on LV remodelling and compare it with primary CRT implantation. We therefore limited our study population to patients in whom echocardiographic follow-up was available at our centres, which may have introduced a selection bias. For the same reason, our study was not suited to comprehensively assess morbidity and mortality endpoints. Very recently, a comparison of heart failure patients undergoing CRT upgrade with primary CRT implantation revealed a similar risk of cardiac events after a mean follow-up of 2.33 and 2.43 years, respectively.[20] The mean duration of RV pacing prior to CRT upgrade, however, was only 2.8 years in this cohort, which is of major importance, because the detrimental effects of RV pacing increase with increasing duration of RV pacing.[9] In contrast, the mean duration of RV pacing in our study was 6.7 years extending up to over 12 years in nine individuals. Interestingly, the benefit of CRT upgrade appeared independent of the duration of previous RV pacing, and a majority of patients even in the latter group responded to CRT. These data indicate that reverse remodelling may occur even after very long periods of RV pacing and hence support the use of CRT even in this setting. As reverse LV remodelling is associated with a favourable prognosis after primary CRT implantation,[7,8] an improvement in survival would equally be expected in this patient population.

In the current study, we only analysed the change in echocardiographic parameters at the maximum follow-up time point available for each patient, and did not perform formal longitudinal analysis of LV remodelling after CRT implantation. We can therefore not unequivocally prove at what time point after implantation the beneficial effect of CRT upgrade begins to set in. However, when patients with different maximum follow-up periods were compared, the degree of echocardiographic improvement (as well as in NYHA functional class) was similar at all time points investigated (data not shown). Hence despite the lack of a formal longitudinal analysis, our data strongly suggest that the beneficial effects of CRT upgrade on echocardiographic reverse remodelling occur early and are sustained, which compares well with the pattern observed after primary CRT implantation.

In addition to the parameters investigated in the present study, further aspects regarding the response to CRT, including the assessment of RV size and function, diastolic dysfunction, and echocardiographic signs of dyssynchrony may be important and of potential interest in the comparison of primary CRT recipients and CRT upgrades. The present retrospective study, however, was primarily designed to assess the effect of CRT on LV function and LV remodelling, and therefore, further studies are needed to address these particular aspects.

# Conclusions

The current study demonstrates that CRT reverses LV remodelling in heart failure patients with chronic RV pacing in a similar way as in primary CRT recipients, even after very long periods of RV pacing. Our data therefore may have important implications for the treatment of pacemaker-dependent patients with heart failure, and support the use of CRT in this setting. Whether this translates into an improved prognosis, in particular for patients with very long-term RV pacing, remains to be determined.

## Acknowledgements

The authors would like to thank Prof. B. Seifert, Department of Biostatistics, University of Zurich for help with the statistics.

**Conflict of interest:** D.H.: Educational grants from Boston Scientific and Medtronic, speaker honoraria, and consulting fees from St Jude Medical. T.F.L.: Educational grants from Biotronik, Medtronic and St Jude Medical. F.R.: Research grants, speaker honoraria, and consulting fees from Biotronik. W.T.A.: Research grants, speaker honoraria, and consulting fees from Medtronic, St Jude

Medical, and Biotronik. J.H.: Consulting fees from St Jude Medical and Biotronik; research grants and speaker honoraria from Biotronik, St Jude and Medtronic.

## References


1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
3. Holzmeister J, Hurlimann D, Steffel J, Ruschitzka F. Cardiac resynchronization therapy in patients with a narrow QRS. *Curr Heart Fail Rep* 2009;**6**:49–56.
4. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* 2006;**113**:266–272.
5. Steendijk P, Tulner SA, Bax JJ, Oemrawsingh PV, Bleeker GB, van Erven L, Putter H, Verwey HF, van der Wall EE, Schalij MJ. Hemodynamic effects of long-term cardiac resynchronization therapy: analysis by pressure–volume loops. *Circulation* 2006;**113**:1295–1304.
6. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
7. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;**53**:483–490.
8. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;**112**:1580–1586.
9. Nielsen JC, Andersen HR, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation* 1998;**97**:987–995.
10. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. *J Am Coll Cardiol* 2006;**48**:1642–1648.
11. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, Girardot R, Crepin D, Reant P, Roudaut R, Jais P, Haissaguerre M, Clementy J, Jimenez M. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 2004;**110**:3766–3772.
12. Maurer G, Torres MA, Corday E, Haendchen RV, Meerbaum S. Two-dimensional echocardiographic contrast assessment of pacing-induced mitral regurgitation: relation to altered regional left ventricular function. *J Am Coll Cardiol* 1984;**3**:986–991.
13. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *J Am Med Assoc* 2002;**288**:3115–3123.
14. Saad EB, Marrouche NF, Martin DO, Cole CR, Dresing TJ, Perez-Lugones A, Saliba W, Schweikert RA, Wilkoff BL, Tchou P, Natale A. Frequency and associations of symptomatic deterioration after dual-chamber defibrillator implantation in patients with ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2002;**90**:79–82.
15. Leon AR, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, Langberg JJ, DeLurgio DB. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002;**39**:1258–1263.
16. Horwich T, Foster E, De Marco T, Tseng Z, Saxon L. Effects of resynchronization therapy on cardiac function in pacemaker patients 'upgraded' to biventricular devices. *J Cardiovasc Electrophysiol* 2004;**15**:1284–1289.
17. Eldadah ZA, Rosen B, Hay I, Edvardsen T, Jayam V, Dickfeld T, Meininger GR, Judge DP, Hare J, Lima JB, Calkins H, Berger RD. The benefit of upgrading chronically right ventricle-paced heart failure patients to resynchronization therapy demonstrated by strain rate imaging. *Heart Rhythm* 2006;**3**:435–442.
18. Witte KK, Pipes RR, Nanthakumar K, Parker JD. Biventricular pacemaker upgrade in previously paced heart failure patients—improvements in ventricular dyssynchrony. *J Card Fail* 2006;**12**:199–204.
19. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;**112**:e154–e235.
20. Nagele H, Dodeck J, Behrens S, Azizi M, Hashagen S, Eisermann C, Castel MA. Hemodynamics and prognosis after primary cardiac resynchronization system implantation compared to 'upgrade' procedures. *Pacing Clin Electrophysiol* 2008;**31**:1265–1271.
21. Bax JJ, Gorcsan J 3rd. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;**53**:1933–1943.
22. Duray GZ, Israel CW, Pajitnev D, Hohnloser SH. Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate. *Europace* 2008;**10**:48–52.
23. Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol* 2008;**52**:438–445.
24. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;**28**:33–41.
25. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;**113**:969–976.